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Brief Report of the Therapeutic Potential of Utilizing the Cannabinoid Receptor in Systemic Sclerosis (SSc)

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Abstract

Marijuana, the herbal preparation of Cannabis sativa, is used by patients within a medical context as a regulator of neurotransmission for analgesia, antianxiety, antiemetic, and anticonvulsive effects. Medical use of cannabis is limited by potential adverse drug effects, including an increase in heart rate, vasodilation, appetite stimulation, dry mouth, dizziness, and possibly acute psychosis. While cannabis may contain many cannabinoid (tricyclic dibenzopyran) compounds, the psychoactive effects are mediated by Δ^9 Tetrahydrocannabinol (THC). The effects of cannabis are primarily exerted through the cannabinoid receptors, CB_1 and CB_2. Cannabimimetics (commonly referred to as synthetic cannabinoids), a group of compounds encompassing a wide range of chemical structures, have been developed by scientists in order to achieve selectivity toward one or both receptors for improved therapeutic activity with reduced adverse effects. This review discusses the potential therapeutic effect of cannabimimetics as it relates to Systemic Sclerosis (SSc) with an emphasis on possible legal and social concerns.

Keywords: Cannabinoid receptor; Systemic sclerosis

Background

The cannabinoids are a group of compounds that either structurally is related to Δ^9-Tetrahydrocannabinol (Δ^9-THC) or that which bind to cannabinoid receptors. Cannabinoids include phytocannabinoids present in *Cannabis sativa*, the marijuana plant; endogenous cannabinoids (endocannabinoids); and synthetic cannabinoids generated in a laboratory. The goal of using these substances medicinally is to achieve therapeutic efficiency for specific pathologic conditions without many side effects. The ability of these compounds to achieve this effect is influenced by selectivity of receptor as well as route of administration and metabolism [1-3].

The cloning of two cannabinoid receptors, CB_1 and CB_2, allows targeting therapeutic, non-psychotropic effects of cannabinoid compounds, since the mechanisms underlying the psychotropic effects have been clearly attributed to CB_1 receptors, abundantly expressed by the vast majority of neurons, while the properties related to immune system modulation, are mediated by CB_2 expressed by immune cells and a restricted population of neurons in the brain stem [4,5]. Cannabinoids modulate fibrogenesis in systemic sclerosis (SSc, scleroderma) [6-8], thus are attractive as possible therapeutic agents for treatment of this condition. However, responsibilities of physicians who prescribe medical marijuana differ from those who prescribe traditional FDA-approved medications and may involve legal risks [9].

Marijuana

Cannabis sativa contains over 80 different chemical constituents [10]. There are three phytocannabinoids: THC, Cannabinol (CBN), and Cannabidiol (CBD). The primary component of cannabis is THC, which is responsible for the psychoactive effects of the plant; it also has mild analgesic and antioxidant activities. CBN is a breakdown product of THC and exerts weaker affects than THC on cannabinoid receptors. CBD is 40% of the extract of medical cannabis. Studies on pharmacokinetics reveal that smoking marijuana provides rapid delivery from the lungs to brain, which contributes to its abuse potential. Sublingual administration reduces first-pass liver metabolism, but results in lower THC levels. Absorption is slowest when cannabinoids are ingested and metabolized by the liver, which results in lower and delayed peak THC concentrations [11].

Endocannabinoids

The endocannabinoid system is comprised of neuromodulatory lipids and receptors. The endogenous ligands-or endocannabinoids-N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) are long-chain fatty acid derivatives lipid transmitters [12]. The first step of endocannabinoid biosynthesis occurs by the conversion of phosphatidylethanolamine into eCBs. Phosphatidylethanolamine, is a membrane-resident phospholipid, which comprises approximately 25% of mammalian phospholipids and is particularly enriched in the brain where the phosphatidylethanolamine content is approximately 45% of total phospholipids [13]. Phosphatidylethanolamine is converted into N-acyl-phosphatidylethanolamine (NAPE), then phospholipase D cleaves NAPE to yield anandamide [14].

Anandamide's effects occur at cannabinoid binding sites throughout the central and peripheral nervous systems and can be either central mediated primarily in the central nervous system by CB_1 receptors in the brain, or in the periphery by CB_2 receptors [5]. The mechanisms underlying the psychotropic effects are attributed to CB_1 receptors, whereas the medicinal properties, especially those related to immune system modulation, are likely mediated by CB_2 [4]. The two distinct physiologic effects of CB_1 and CB_2 receptors have resulted synthetic cannabinoid development.

Synthetic cannabinoids

Cannabimimetic compounds are synthetic cannabinoids can be chemically classified into major structural groups: naphthoylindoles, benzoylindoles, phenylacetylindoles, adamantylindoles, cyclophenols and a miscellaneous group [3]. In general, the compounds that show little selectivity between CB_1 and CB_2 are classified as general agonists, while compounds which are agonists that are highly selective for either CB_1 versus CB_2 with greater than one hundred fold selectivity is a selective agonist [10]. While the specific chemistry, toxicity, and pharmacology of these compounds are beyond the scope of this review, the selectivity toward one or both receptors for improved therapeutic activity with reduced adverse effects has specific legal and social concerns.

Medical practitioners who prescribe marijuana (a Schedule I controlled substance) for medical use, should be careful in making their decision, considering federal law and professional regulations, and should consult with legal experts [9]. It is a challenge for medical professionals to navigate the complexities of state and federal laws in order to prescribe medical marijuana. In the United States (U.S.), medical marijuana use was first reduced in 1970, when the Controlled Substances Act listed marijuana as a Schedule I substance with no medical value and with a high potential for abuse [9]. The Department of Veterans Affairs supports this position by prohibiting the use of medical marijuana in its facilities. The Department of Justice, declares that the selling, cultivation, or distribution of marijuana is against federal law. In 2002, the U.S. Court of Appeals held that the First Amendment, which protects free speech, allows physicians to discuss and perhaps recommend medical marijuana use without punishment [9].

In the states that allow the use of medical marijuana, physicians may only "recommend" its use or "advise consideration" of such therapy; they are not allowed to "prescribe" it. Physicians may choose to document this recommendation in the medical record and provide a copy to the patient or provide written proof of therapeutic need on an official form in States that allow its prescription. Physicians' legal exposure may be protected by confidentiality laws pertaining to medical records, such as the Health Insurance Portability and Accountability Act (HIPAA) [9]. Legislatures in many countries are creating novel forms of regulation separate from domestic drug laws; however, internationally medical marijuana use is complicated by regulatory inconsistencies and ambiguities [15].

Cannabinoid-like receptors

Substances that do not directly act on cannabinoid receptors, such as a structural analog of endocannabinoid anandamide, the fatty acid Palmitoylethanolamide (PEA) may be an attractive option for physician use. PEA has affinity to cannabinoid-like G-coupled receptors (GPR55 and GPR119), without the potential negative effects of synthetic cannabinoids [16]. PEA has been demonstrated to bind to a receptor in the cell-nucleus (a nuclear receptor), with the main target thought to be the peroxisome proliferator-activated receptor alpha (PPAR-α) [17,18]. PEA is not a classic endocannabinoid because it lacks affinity for the cannabinoid receptors CB_1 and CB_2, but by preventing the metabolism of other endocannabinoids it may enhance anandamide and provide synergistic effects for modulation of pain. PEA may inhibit peripheral inflammation and mast-cell degranulation, as well as to exert neuroprotective and antinociceptive [19].

Relevance to systemic sclerosis

Systemic sclerosis (SSc, scleroderma) is an autoimmune disease characterized by vasculopathy and fibrosis. Whilst SSc may be heterogeneous in both severity and organ-involvement, progressive skin thickening is not only a key diagnostic characteristic [20] but, results in severe symptomatology which results in intense discomfort from burning and pruritus. SSc patients have a considerable prevalence of pedal peripheral neuropathy [21]. A reduction of sensory and autonomic innervation in both sclerotic and apparently uninvolved skin has been reported in SSc [22] with mast cell association early in the pathologic process [23]. SSc may reduce the number of nerve endings or make them more sensitive. This hypothesis raises the possibility that SSc-itch may be peripherally neurogenic in nature and may change over time and with disease severity [24]. Treatment of these skin symptoms are challenging, as to date there are no proven therapies that are consistently effective, though immunosuppressive agents are thought to have some positive effect [25].

High quality clinical trials of drug therapies to prevent or treat itching in palliative care are reviewed as a meta-analysis, but this Cochrane review does not discuss the cannabinoids as potential neuronal modulators of itch [26]. Potential side effects of treatment for skin symptoms are particularly important in SSc as the main goal for pruritus management is improving patient quality of life.

While itch in SSc has not been extensively studied, investigators are able to demonstrate that cannabinoids have an anti-fibrotic activity, thereby possibly representing a new class of agents targeting fibrotic diseases [27]. In mouse models, the cannabinoid receptor CB_1 is crucial for leukocyte infiltration and secondary fibroblast activation and inactivation of CB_1 exerts potent anti-fibrotic effects in inflammation-driven models of fibrosis [28]. Synthetic cannabinoids are capable of preventing skin fibrosis in experimental models of SSc [29-31]. Further studies in patients with SSc are needed.

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